MET, RAF and NTRK

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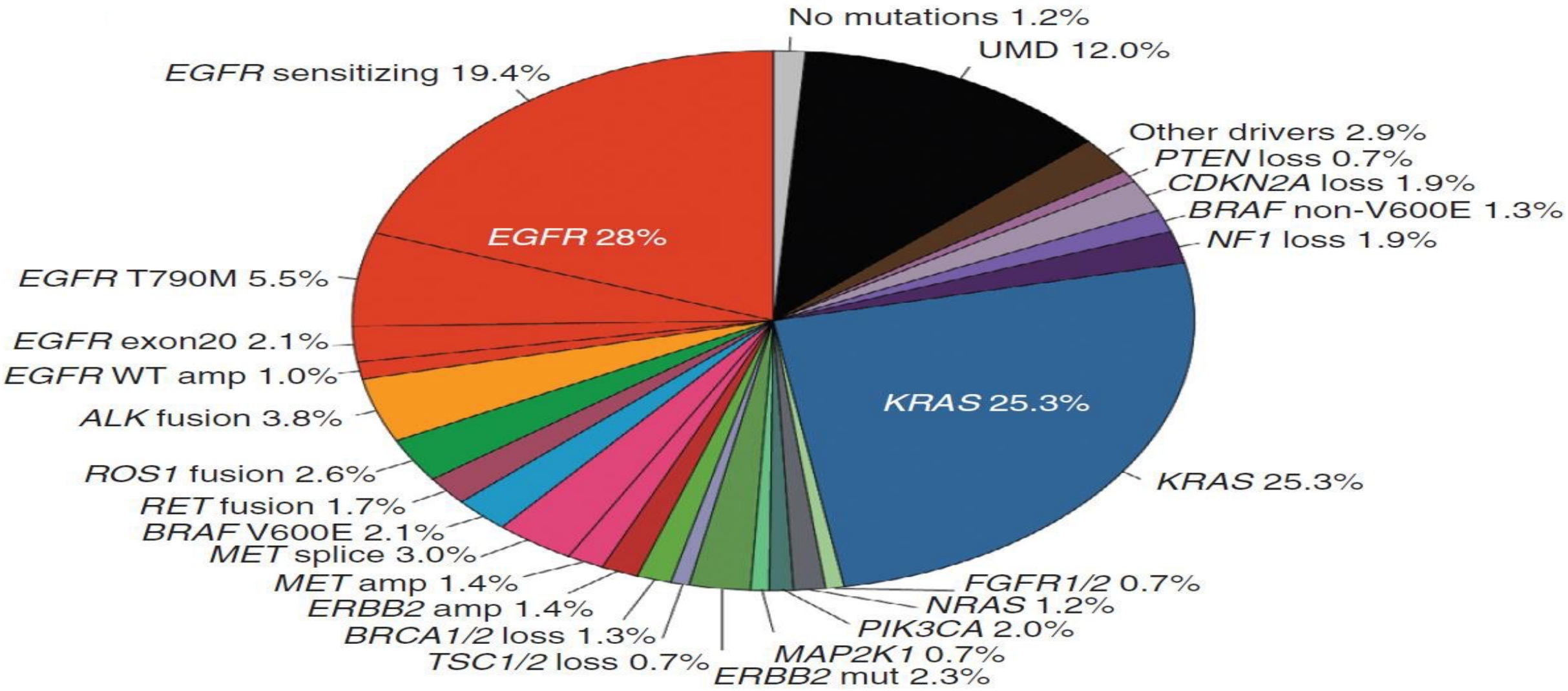
MARCH 1-3, 2024

13TH WINTER CANCER SYMPOSIUM

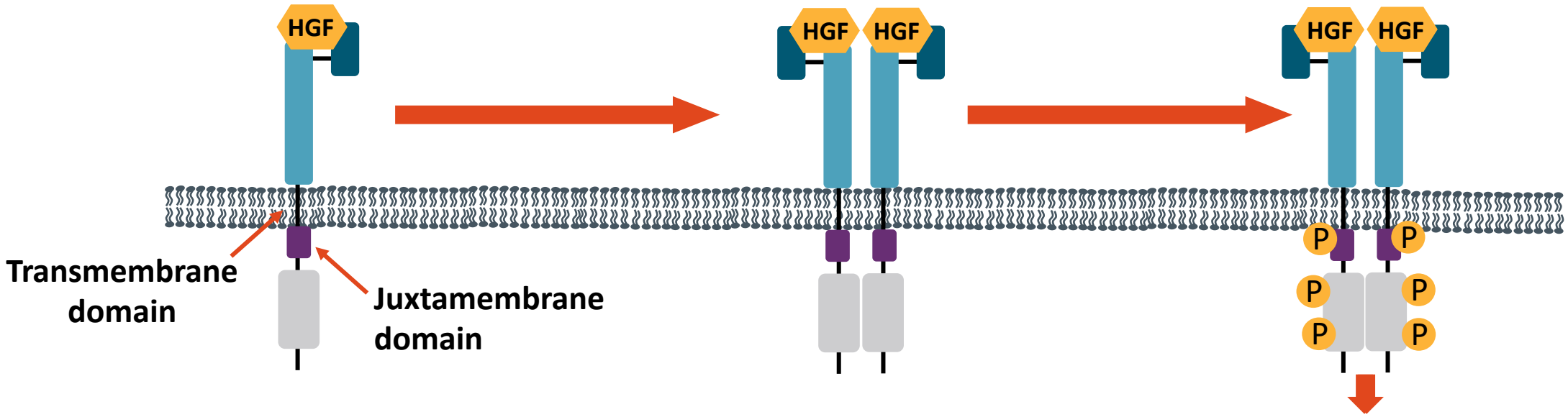
Accredited by:

Rare Targets in NSCLC



Jordan EJ et al. *Cancer Discov*. 2017;7(6):596-609.

Wild-Type MET Signaling



Recruitment of signaling proteins

- Survival
- **Decreased apoptosis**
- Regulation of cytoskeletal functions
- **Growth**
- **Differentiation**
- **Stemness**

Salgia. Cancer Treat Rev. 2020;87:102022.

Slide credit: clinicaloptions.com

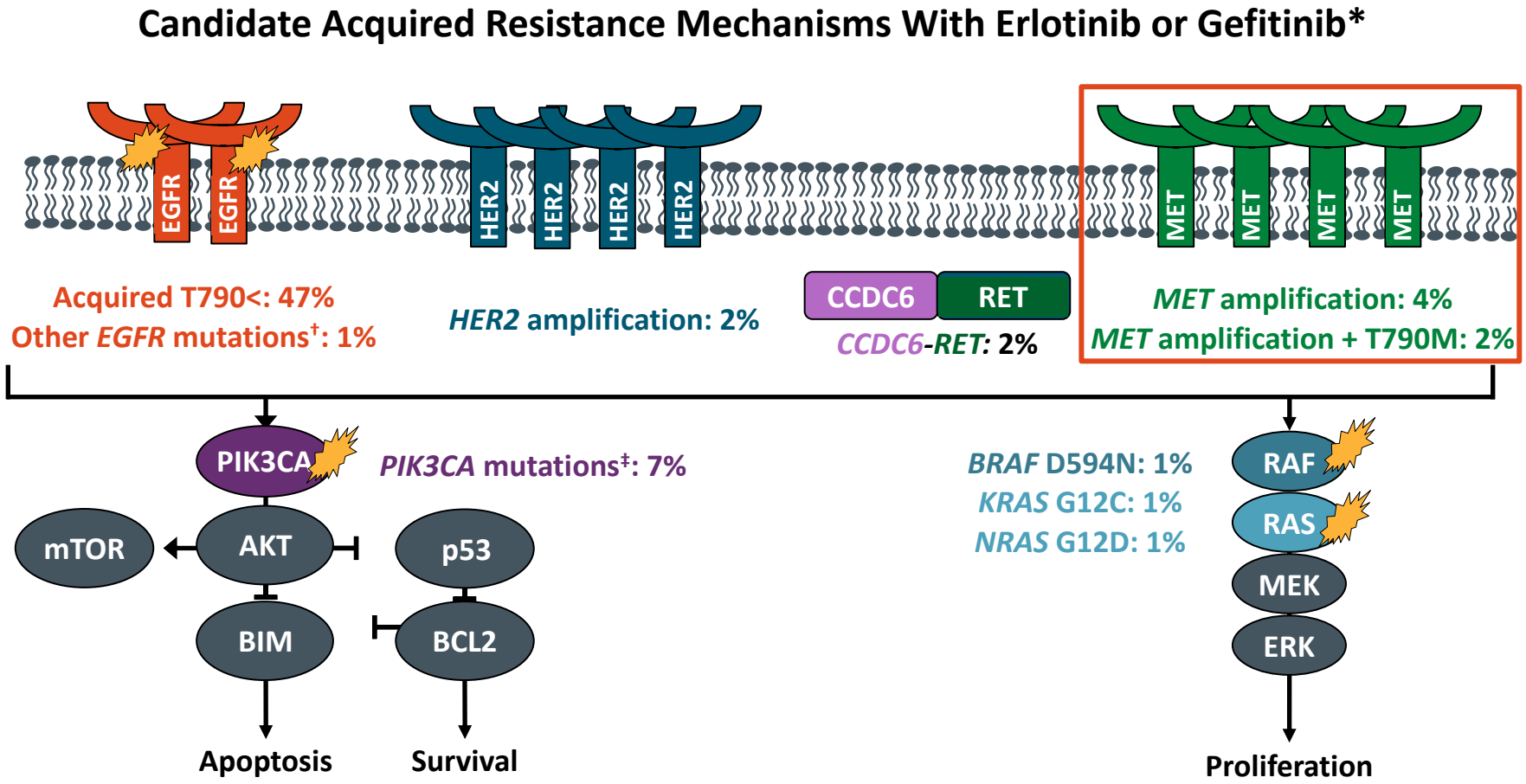
MET Aberrations in Cancer: Structural Alterations and Oncogene Addiction

- MET activation occurs via several mechanisms, including *MET*ex14 skipping mutations and *MET* amplification[1,2]
  - Patient subgroups need to be well characterized
- Types of *MET* aberrations[3]
  - Single nucleotide variants
  - Amplification
  - Exon 14 skipping mutation
  - Fusions

1. Van der Steen. J Thorac Oncol. 2016;11:1423. 2. Drilon. J Thorac Oncol. 2017;12:15. 3. Comoglio. Nat Rev Cancer. 2018;18:341.

FLAURA Paired Plasma NGS: Acquired Resistance Mechanisms With Erlotinib or Gefitinib

- NGS analysis of paired plasma samples at BL and following PD on erlotinib or gefitinib (n = 129)
- Most common acquired resistance mechanisms identified:
  - *EGFR* T790M
  - *MET* amplification
  - *HER2* amplification



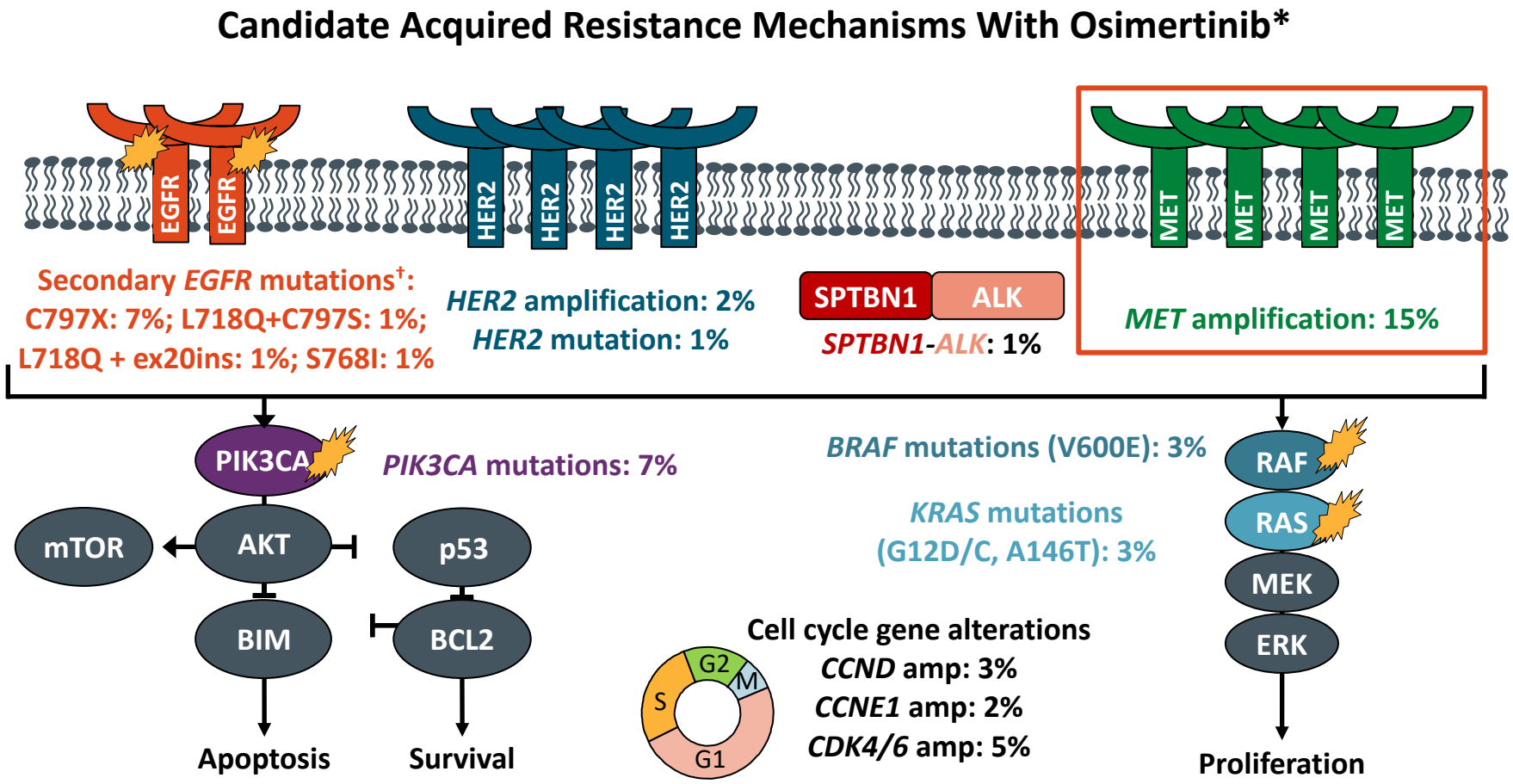
*Overlap of reported resistance mechanism may occur. †Acquired T790M + C797S + L718Q: 1%. ‡PIK3CA + T790M (n = 1), PIK3CA + T790M + C797S (n = 1), and PIK3CA (n = 1).

Ramalingam. ESMO 2018. Abstr LBA50.

Slide credit: clinicaloptions.com

FLAURA Paired Plasma NGS: Acquired Resistance Mechanisms With Osimertinib

- NGS analysis of paired plasma samples at BL and following PD on osimertinib (n = 91)
- No evidence of acquired *EGFR* T790M
- Most common resistance mechanisms:
  - *MET* amplification
  - *EGFR* C797S mutation
- Other mechanisms included *HER2* amplification, *PIK3CA*, and *RAS* mutations



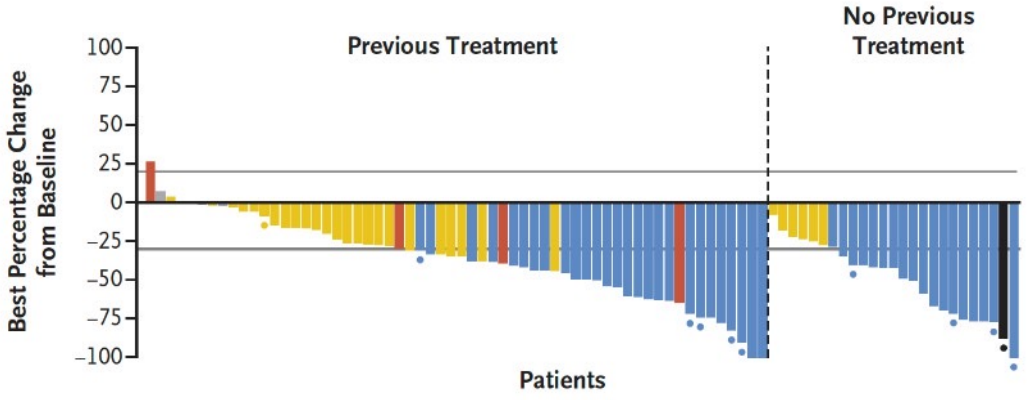
*Overlap of reported resistance mechanism may occur. †n = 2 with de novo T790M mutations at BL; 1 acquired C797S at progression.

Ramalingam. ESMO 2018. Abstr LBA50.

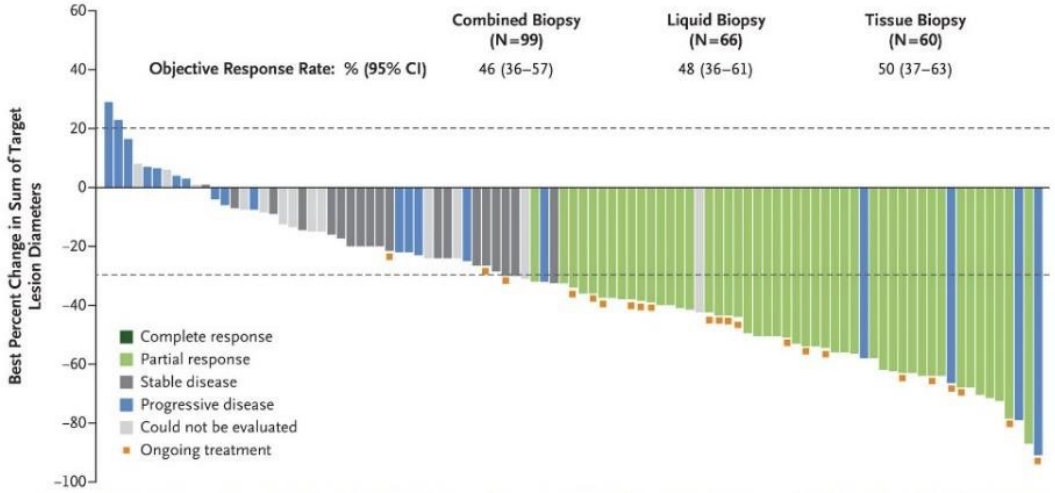
Slide credit: clinicaloptions.com

MET exon 14 Skipping Mutation-Positive NSCLC

Capmatinib



Tepotinib



	Line of Treatment	N	ORR, %	DOR	Median PFS (Month)
Capmatinib	1L	60	66.7	12.6	12.3
	2-3L	100	44.0	9.7	5.5
Tepotinib	1L	164	57.3	46.4	12.6
	2-3L	149	45.0	12.6	11.0

Wolf J et al. *N Engl J Med*. 2020;383(10):944-957. Paik PK et al. *N Engl J Med*. 2020;383(10):931-943.
Wolf J et al. 2021 ASCO Annual Meeting. Abstract 9020. Mazieres J et al. *JAMA Oncol*. 2023;9(9):1260-1266.

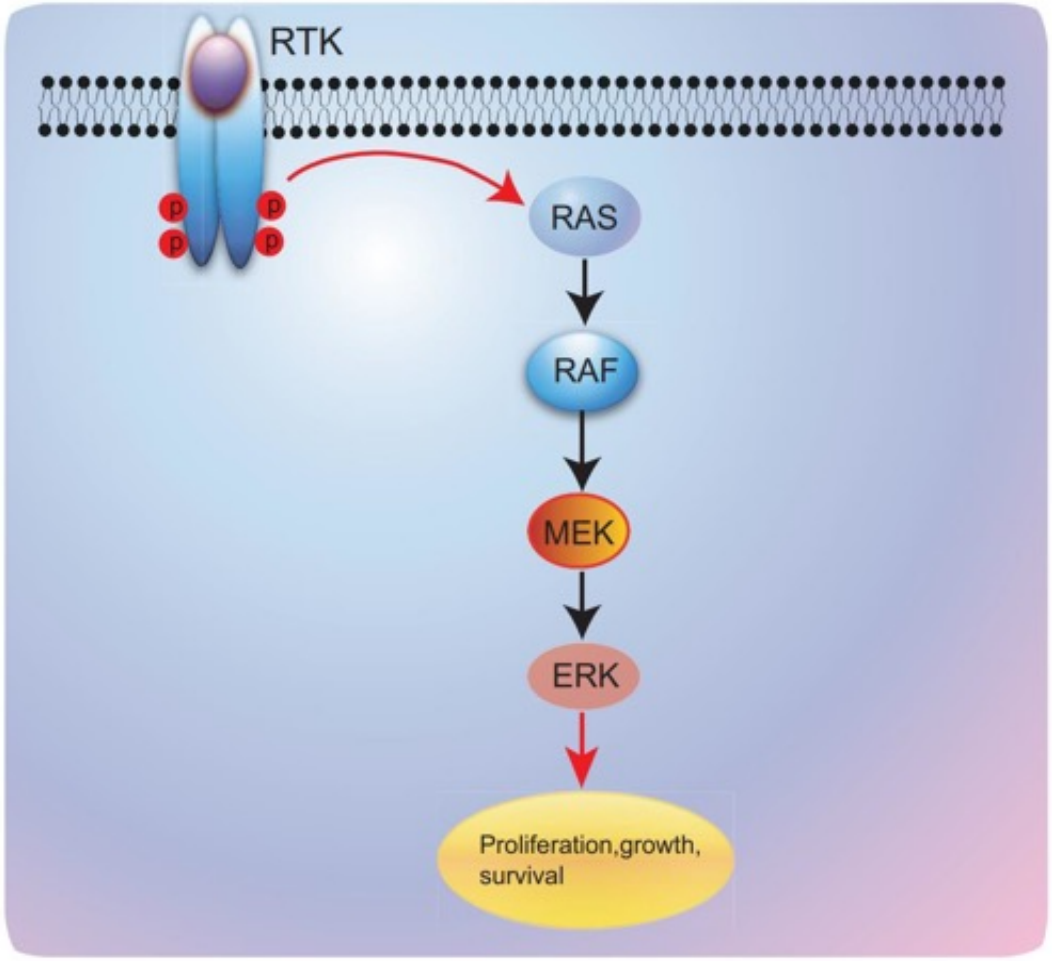
MET ADC on the Horizon

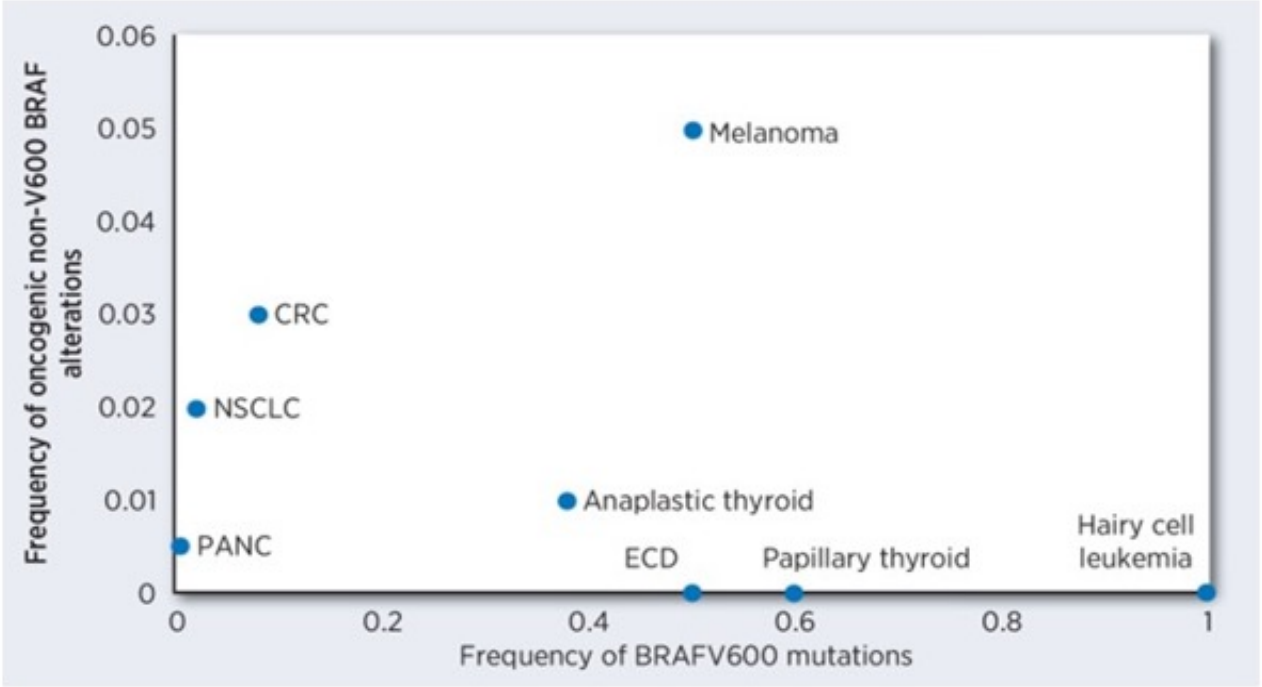
- Phase 2 LUMINOSITY
  - Telisotuzumab-vedotin c-MET antibody-drug conjugate
  - ORR: 35 and 23% in c-Met High and c-Met Intermediate NSCLC, respectively
  - Median OS: 14.6 months and 14.2 months in c-Met High and c-Met Intermediate NSCLC, respectively

- Phase 3 TeliMET-NSCLC-01
  - Telisotuzumab-vedotin vs. docetaxel in previously treated c-Met overexpressing EGFR wild type nonsquamous NSCLC

Abbv ie. Updated Nov ember 29, 2023. Accessed January 26, 2024. https:// news.abbv ie.com/2023-11-29-AbbVie-Announces-Positiv e-Topline-Results-f rom-Phase-2-LUMINOSITY -Trial-Ev aluating-Telisotuzumab-Vedotin-Teliso-V-f or-Patients-with-Prev iously -Treated-Non-Small-Cell-Lung-Cancer -NSCLC

B-RAF Mutations



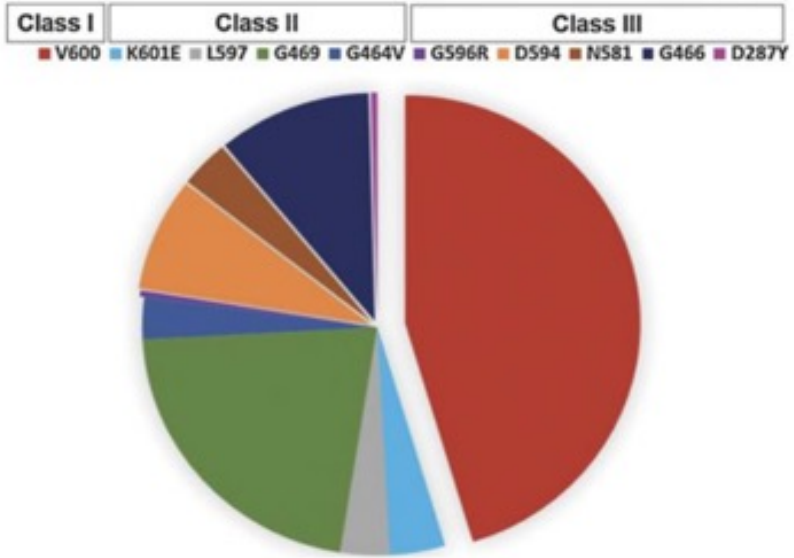


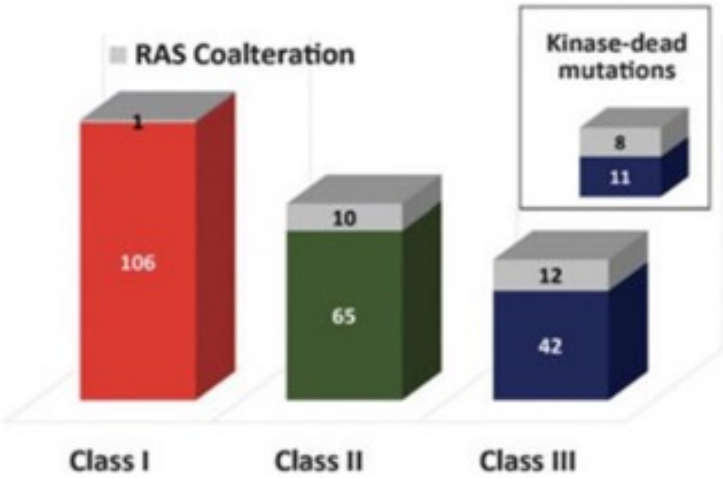
- B-RAF mutations occur in 6-8% of all cancer.
- B-RAF mutations in 2% of lung adenocarcinomas
- 40%- B-RAF V600
- 60%- B-RAF non-V600

Yan et al. Frontiers in Oncology 2022; Poulikakos et al. Clin Cancer Res 2022.

B-RAF Mutant NSCLC

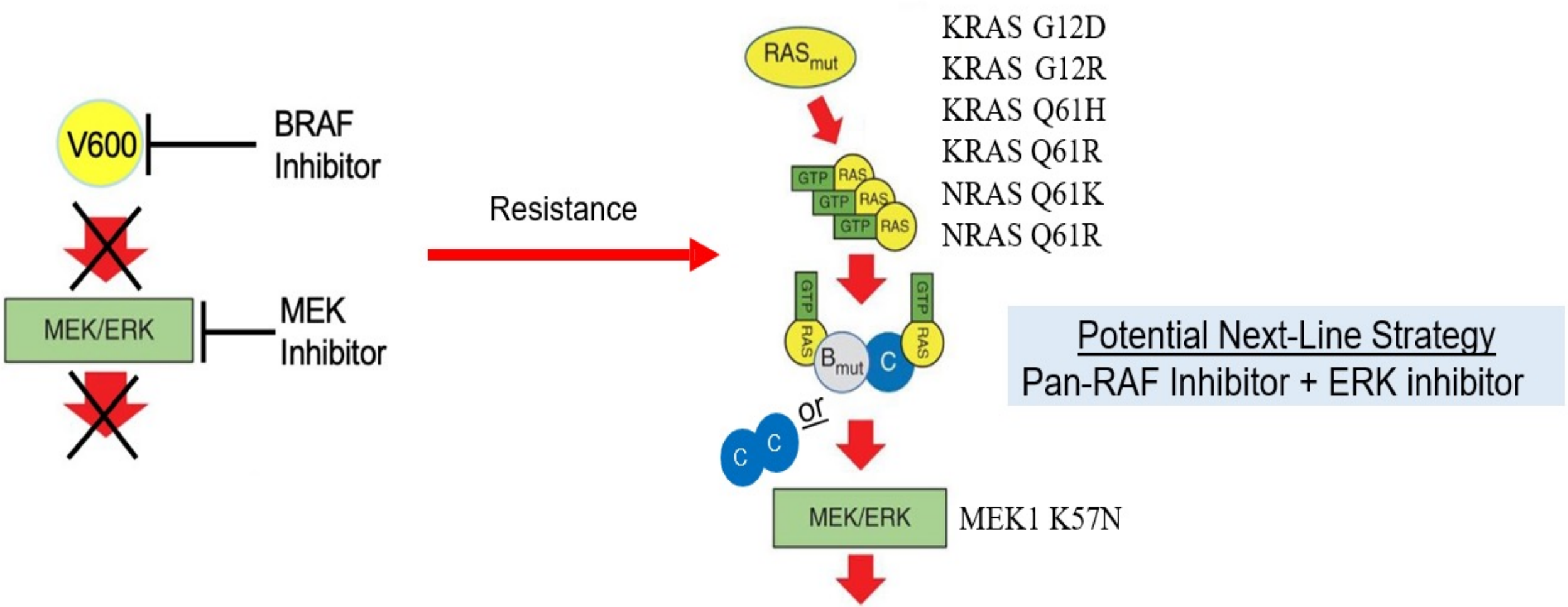
- Characterization of 236 BRAF-mutant NSCLC
  - 107 class I (45%), 75 class II (32%), 54 class III (23%)
  - Never smokers- Class I- 22%, Class II- 3%, Class III- 6%
  - Class II/III more likely to have KRAS co-mutation, brain mets, worse clinical outcomes (PFS, OS) and shorter PFS with platinum based chemotherapy





Dagogo-Jack. Clin Cancer Res 2019

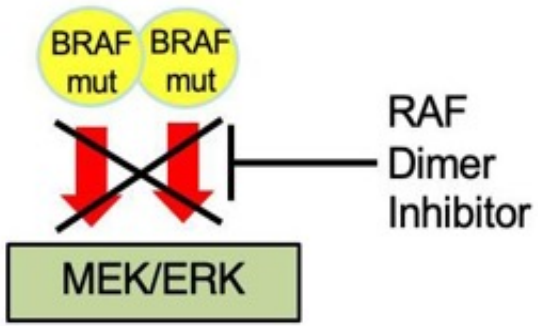
Resistance to Dabrafenib + Trametinib in V600^{mut} NSCLC

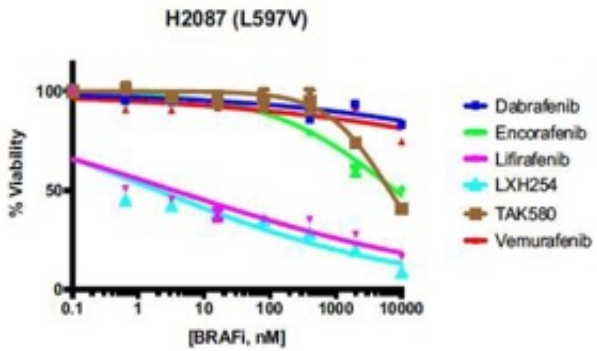


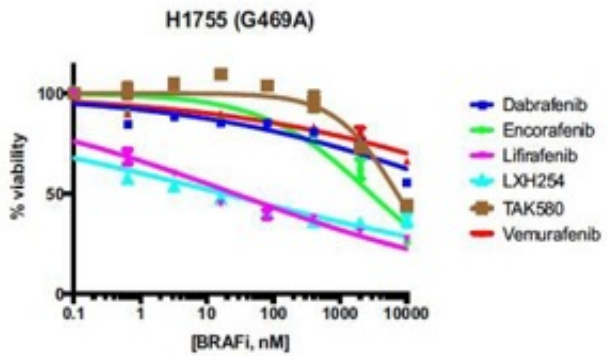
Ortiz Cuaran. Clin Cancer Res 2020; Sheikine. JCO Precision Oncology 2018; Facchinetti. Eur J Cancer 2020; Abravanel. J Tho Oncol 2018; Yaeger. Cancer Discovery 2019.

Other Strategies for Disrupting Signaling in Class II BRAF^{mut}

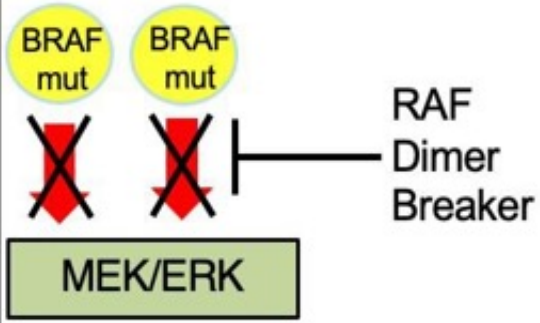
BRAF Dimer Inhibitor (e.g., Lifirafenib and LXH254)

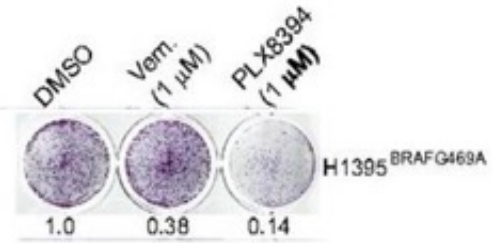


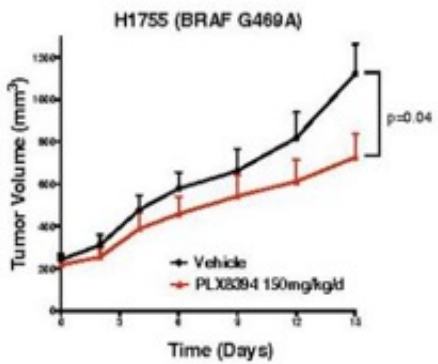


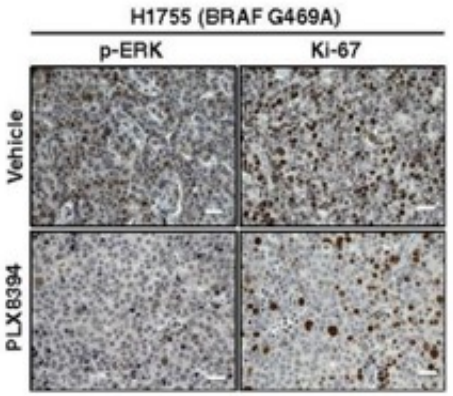


RAF Dimer Breaker (e.g., PLX8394)



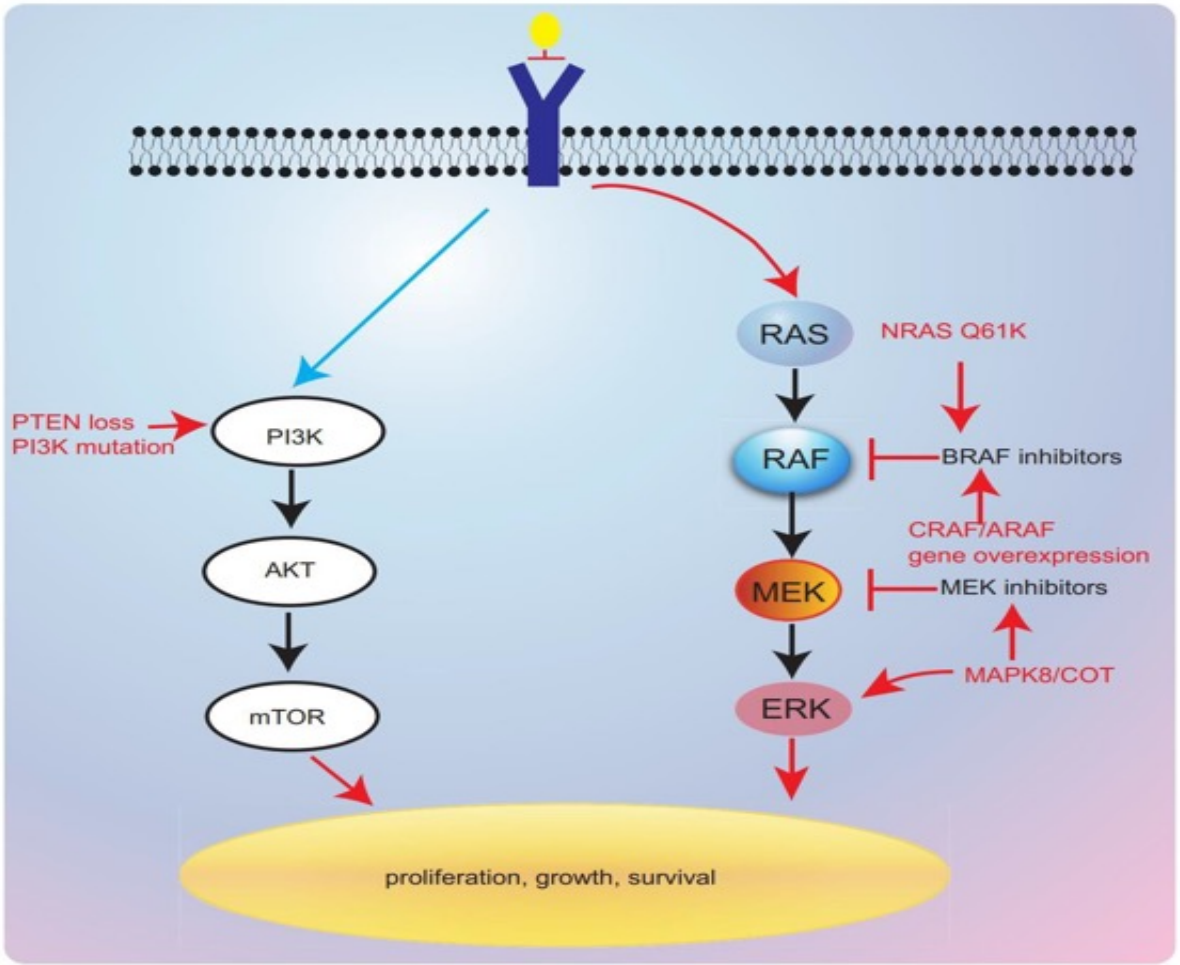






Negrao. J Thor Oncol 2020; Okimoto. PNAS 2016.

Resistance to First Generation B-RAF Inhibitors



Mechanisms of Resistance

1. Kras, NRAS mutations
2. CRAF/ARAF overexpression
3. Increased levels of Braf homodimers
4. MEK mutations
5. PTEN Loss

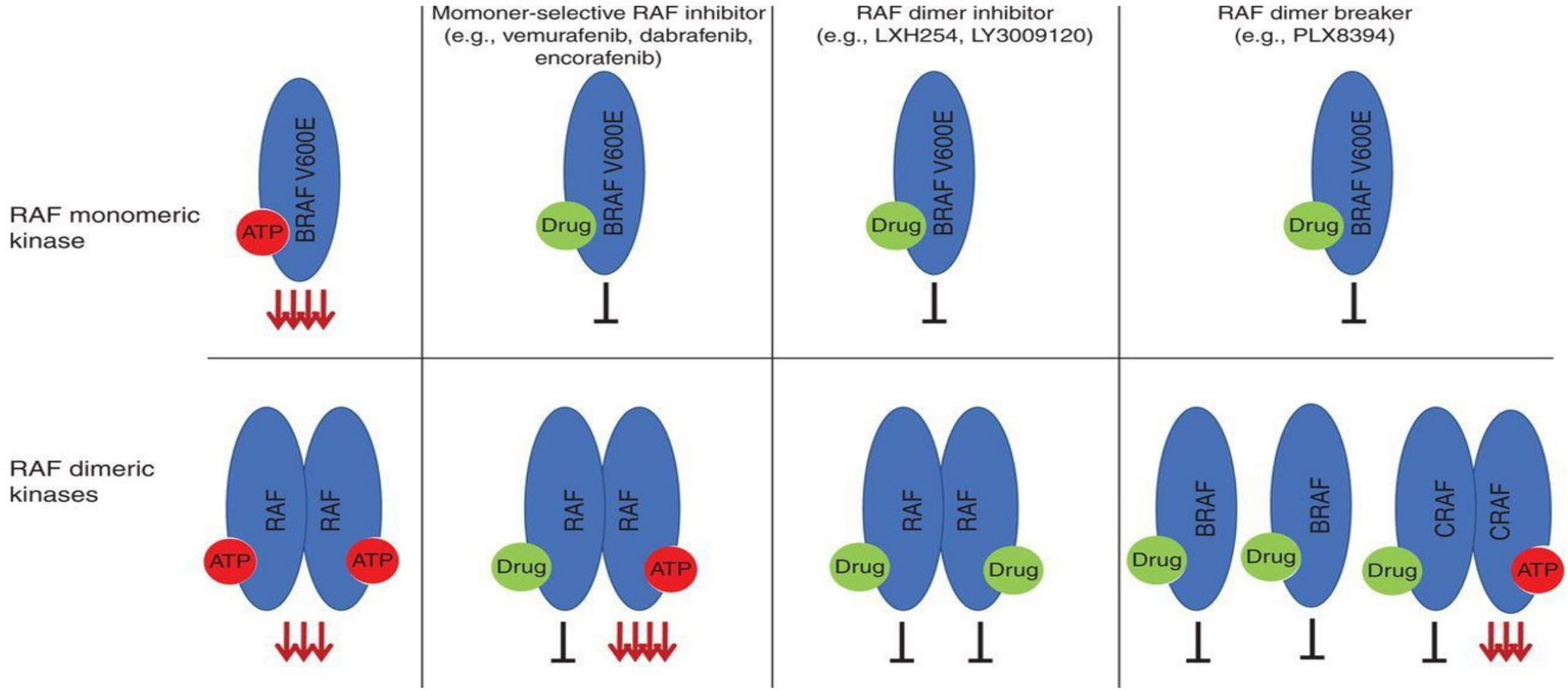
Yan et al. Frontiers in Oncology 2022; Riudavets et al. Lung Cancer 2022

Pan-RAF Inhibitors

- An orally available inhibitor of all members of the Raf family, including A-Raf, B-Raf and C-Raf protein kinases- NCI definition
  - Current B-Raf inhibitors can inhibit A-Raf and C-Raf. But limited since they inhibit monomers and can induce paradoxical activation.

- Next generation Pan-RAF inhibitors:
  - Monomer-selective but do not induce paradoxical activation.
    - FORE8394
  - Equipotent for monomers and dimers
    - LY3009120, BGB-283
  - Dimer selective
    - Belvarafenib, LXH254

Targeting Alterations in the RAF–MEK Pathway



Yaeger R, Corcoran RB. Cancer Discov 2019; 9(3):329-341.

Abstract 9018

Efficacy and safety of encorafenib plus binimetinib in patients with metastatic *BRAF* V600E-mutant (*BRAF*^{V600E}) non-small cell lung cancer (NSCLC) from the phase 2 PHAROS study

Gregory J. Riely,[1] Egbert F. Smit,[2] Myung-Ju Ahn,[3] Enriqueta Felip,[4] Suresh S. Ramalingam,[5] Anne Tsao,[6] Melissa Johnson,[7] Francesco Gelsomino,[8] Raymond Esper,[9] Ernest Nadal,[10] Michael Offin,[1] Mariano Provencio,[11] Gregory A. Otterson,[12] Ibiayi Dagogo-Jack,[13] Ann Alcasid,[14] Tiziana Usari,[15] Keith Wilner,[16] Nuzhat Pathan,[16] Bruce E. Johnson[17]

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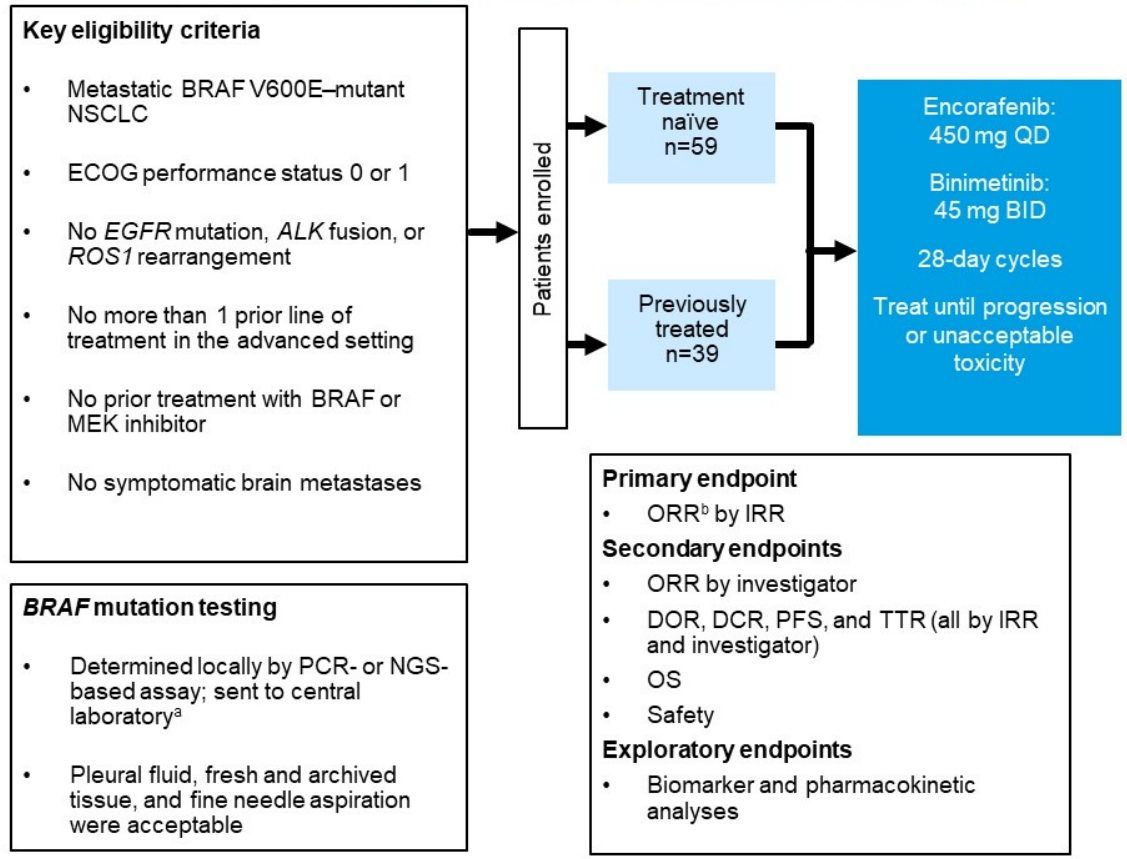
Presented at the 2023 ASCO Annual Meeting, June 2-6, 2023; Chicago, IL, and Online
Correspondence: Gregory Riely, rielyg@MSKCC.ORG

Encorafenib plus binimetinib in patients with metastatic BRAF V600E NSCLC

- The combination of encorafenib (BRAF inhibitor) plus binimetinib (MEK inhibitor) has demonstrated clinical efficacy with an acceptable safety profile in patients with metastatic BRAF V600E/K–mutant melanoma[1]
- For patients with metastatic BRAF V600E–mutant NSCLC the combination of dabrafenib and trametinib was approved by the US FDA and is a current standard of care [2]
  - This approval was based on the results of a single-arm, phase 2 study that showed meaningful antitumor activity and a manageable safety profile[3,4]
    - In treatment-naïve and previously treated patients, the ORR by IRR was 64% and 63%, respectively
    - The median DOR by IRR was 15.2 months and 9.0 months, respectively
- Given the observed efficacy and safety profile of encorafenib plus binimetinib in patients with BRAF V600E/K–mutant metastatic melanoma, this combination therapy was assessed in patients with metastatic BRAF V600E–mutant NSCLC

PHAROS (NCT03915951):
A single-arm, open-label, multicenter, phase 2 study



BID, twice daily; **DCR**, disease control rate; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **IRR**, independent radiology review; **ORR**, objective response rate; **NGS**, next-generation sequencing; **OS**, overall survival; **PCR**, polymerase chain reaction; **PFS**, progression-free survival; **QD**, once daily; **TTR**, time to response.

[a]BRAF V600 mutations were retrospectively confirmed by FoundationOne CDx (Foundation Medicine, Cambridge, MA). [b]According to RECIST 1.1.

1. Dummer R, et al. *Lancet Oncol*. 2018;19(5):603-615. 2. Dabrafenib prescribing information. June 2022. 3. Planchard D, et al. *Lancet Oncol*. 2016;17(7):984-993. 4. Planchard D, et al. *Lancet Oncol*. 2017;18(10):1307-1316.

Encorafenib plus binimetinib in metastatic BRAF-V600E mutant NSCLC

Antitumor activity endpoints by IRR

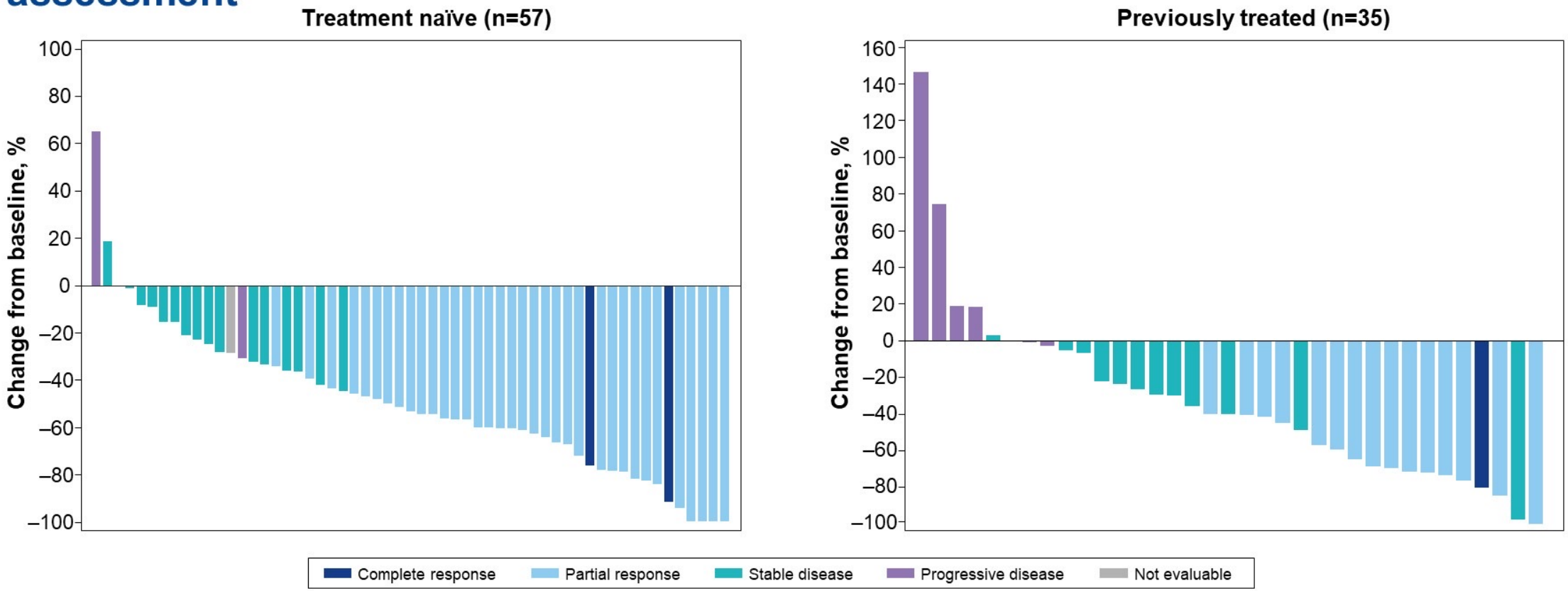
	Treatment naïve (n=59)	Previously treated (n=39)
Objective response rate (95% CI), %[a]	75 (62, 85)	46 (30, 63)
Complete response	9 (15)	4 (10)
Partial response	35 (59)	14 (36)
Stable disease	10 (17)	13 (33)
Progressive disease	2 (3)	3 (8)
Disease control rate at 24 weeks (95% CI), %	64 (51, 76)	41 (26, 58)
Duration of response, median (95% CI), months	NE (23.1, NE)	16.7 (7.4, NE)
Duration of response ≥12 months, n/N (%)	26/44 (59)	6/18 (33)
Time to response, median (range), months	1.9 (1.1-19.1)	1.7 (1.2-7.3)

IRR, independent radiology review; **NE**, not estimable.

[a]Response of 3 patients were not evaluable in the treatment-naïve group, and 5 were not evaluable in the previously treated group.

Encorafenib plus binimetinib in metastatic BRAF-V600E mutant NSCLC

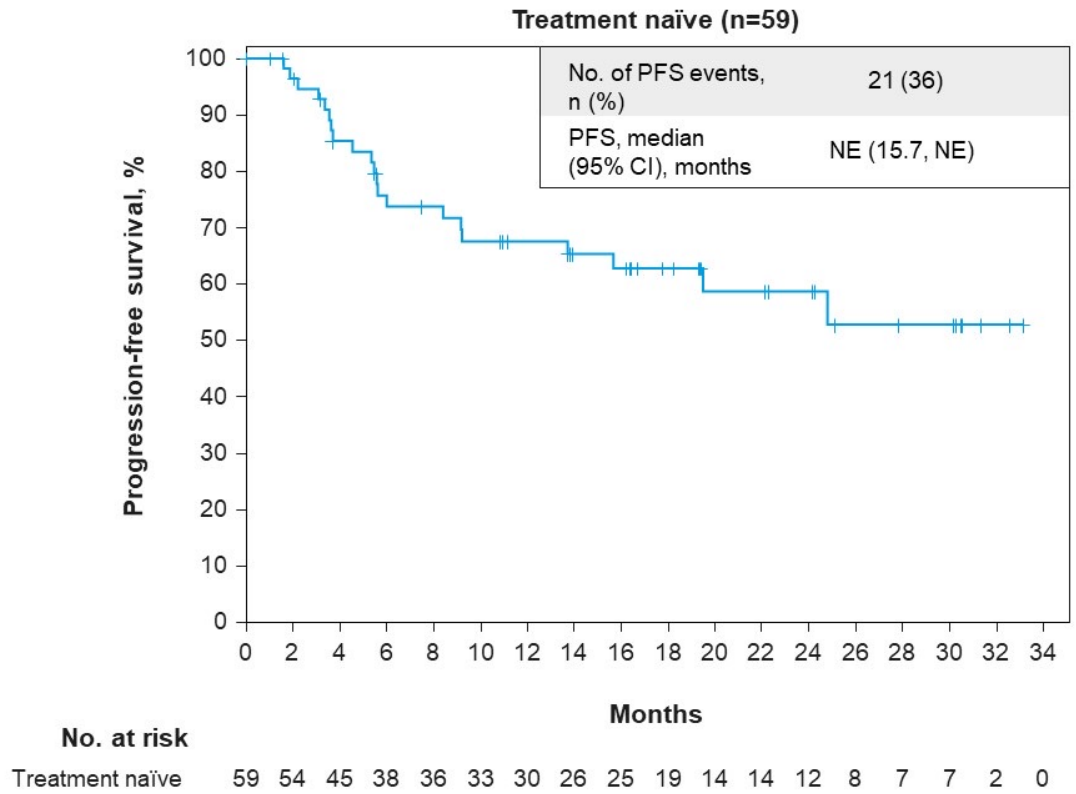
Change from baseline in the sum of diameters of target lesions by investigator assessment[a]

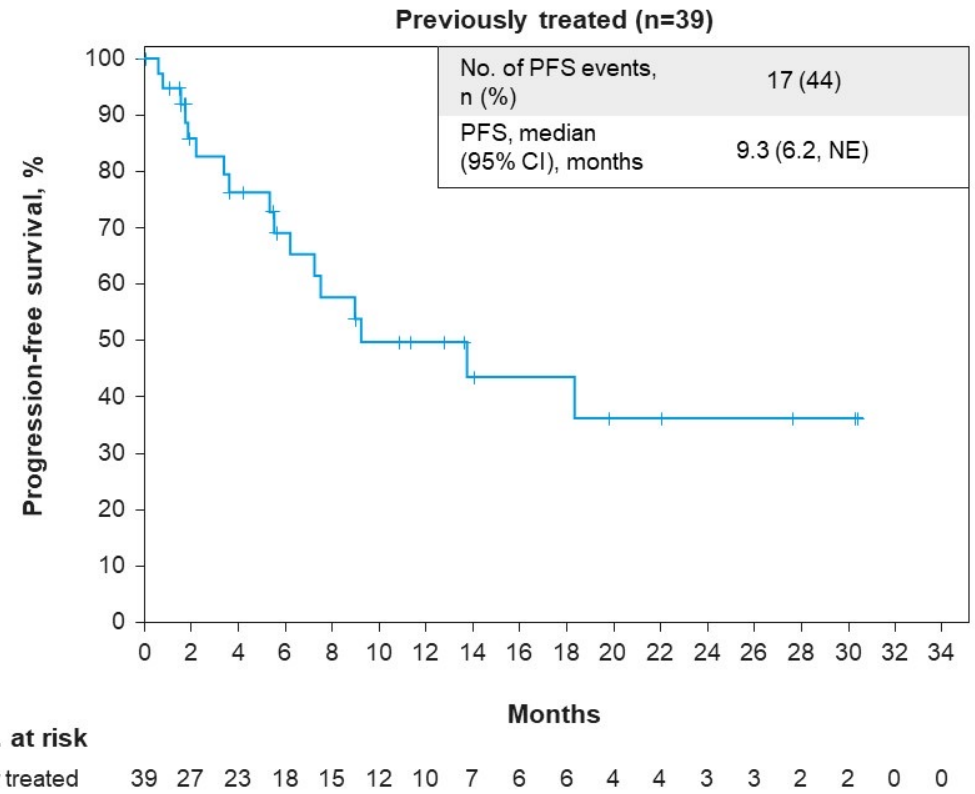


[a]Patients for whom an assessment response was not evaluable at all tumor assessments were not included in this analysis.

Encorafenib plus binimetinib in metastatic BRAF-V600E mutant NSCLC

Progression-free survival by IRR





- The median duration of follow-up for PFS by IRR was 18.2 months (95% CI, 16.4, 22.3 months) in treatment-naïve patients and 12.8 months (95% CI, 9.0, 19.8 months) in previously treated patients

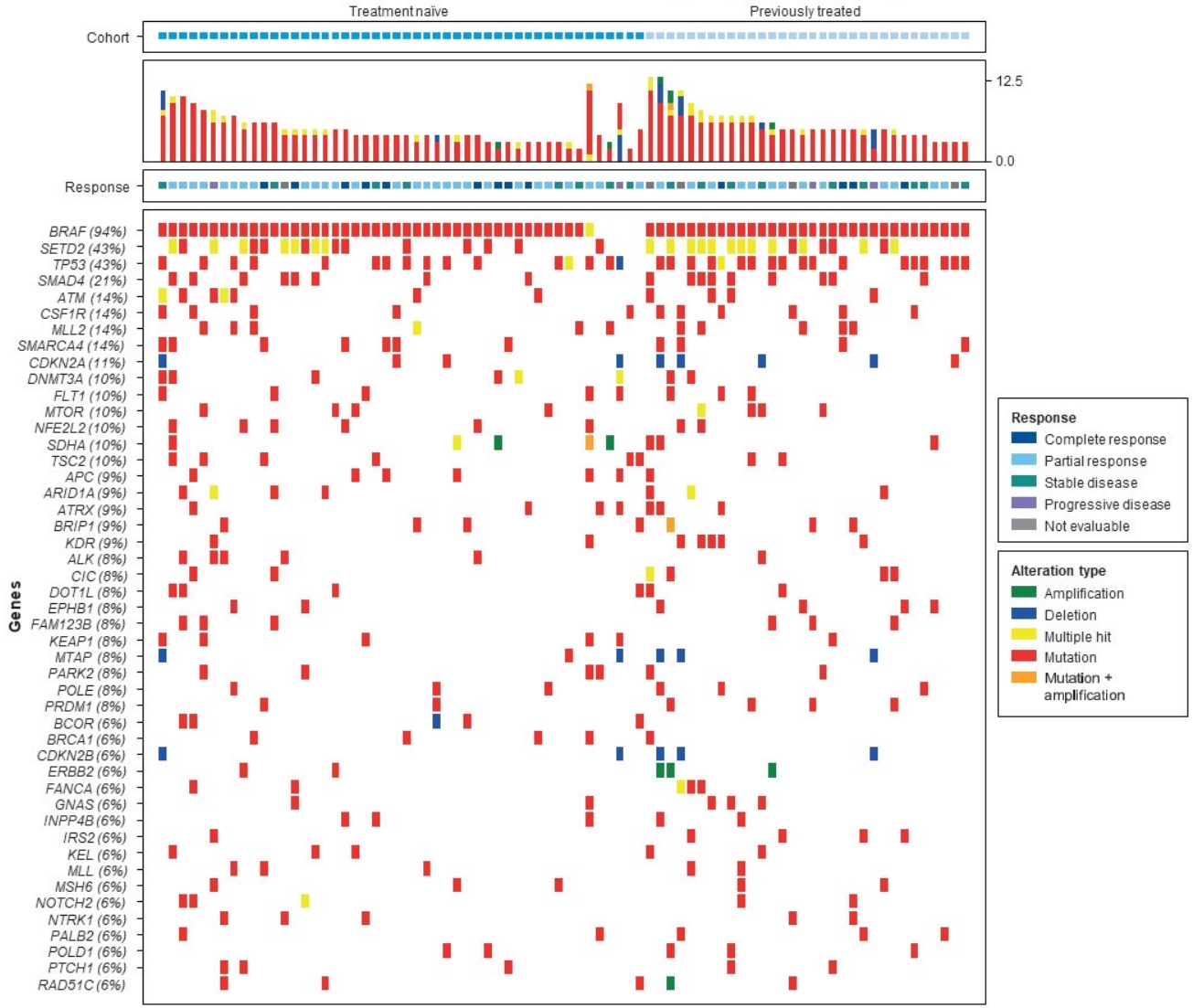
IRR, independent radiology review; **NE**, not estimable; **PFS**, progression-free survival.

Encorafenib plus binimetinib in metastatic BRAF-V600E mutant NSCLC
Incidence of TRAEs of any grade >10% in all patients

	Overall (N=98)		
	Any grade	Grade 3	Grade 4
Any TRAEs, n (%)[a]	92 (94)	37 (38)	3 (3)[b]
Nausea	49 (50)	3 (3)	0
Diarrhea	42 (43)	4 (4)	0
Fatigue	31 (32)	2 (2)	0
Vomiting	28 (29)	1 (1)	0
Anemia	18 (18)	3 (3)	0
Vision blurred	17 (17)	1 (1)	0
Constipation	13 (13)	0	0
ALT increased	12 (12)	5 (5)	0
AST increased	12 (12)	7 (7)	0
Pruritus	12 (12)	0	0
Blood creatine phosphokinase increased	11 (11)	0	0
Edema peripheral	11 (11)	0	0

Note: Any-grade abdominal pain, alopecia, asthenia, and dry skin occurred in 10% of patients; any-grade pyrexia occurred in 8% of patients.
ALT, alanine aminotransferase; **AST**, aspartate aminotransferase; **TRAE**, treatment-related adverse event.
[a]One patient died due to intracranial hemorrhage, which was assessed as treatment related by the investigator. [b]Grade 4 TRAEs were colitis, disseminated intravascular coagulation, increased γ-glutamyl transferase, and hyponatremia.

Encorafenib plus binimetinib in metastatic BRAF-V600E mutant NSCLC
Tumor molecular alterations in baseline biopsy samples[a]



[a]The most frequently altered genes (altered in 5 or more cases) are shown.

Encorafenib plus binimetinib in metastatic BRAF-V600E mutant NSCLC
Conclusions

- The combination of encorafenib plus binimetinib showed a meaningful clinical benefit with an acceptable safety profile in patients with BRAF V600E–mutant metastatic NSCLC in the phase 2 PHAROS study
  - Efficacy was observed in both cohorts:
    - ORRs by IRR were 75% (95% CI: 62-85%) in treatment –naïve patients and 46% (95% CI: 30-63%), in previously treated patients
    - Median DORs by IRR were NE (95% CI, 23.1 months, NE) and 16.7 months (95% CI, 7.4 months, NE), respectively
  - The safety profile was consistent with that observed in the approved indication in melanoma
- Encorafenib plus binimetinib represents a potential new treatment option for patients with BRAF V600E–mutant metastatic NSCLC

IRR, independent radiology review; **NE**, not estimable; **ORR**, objective response rate.

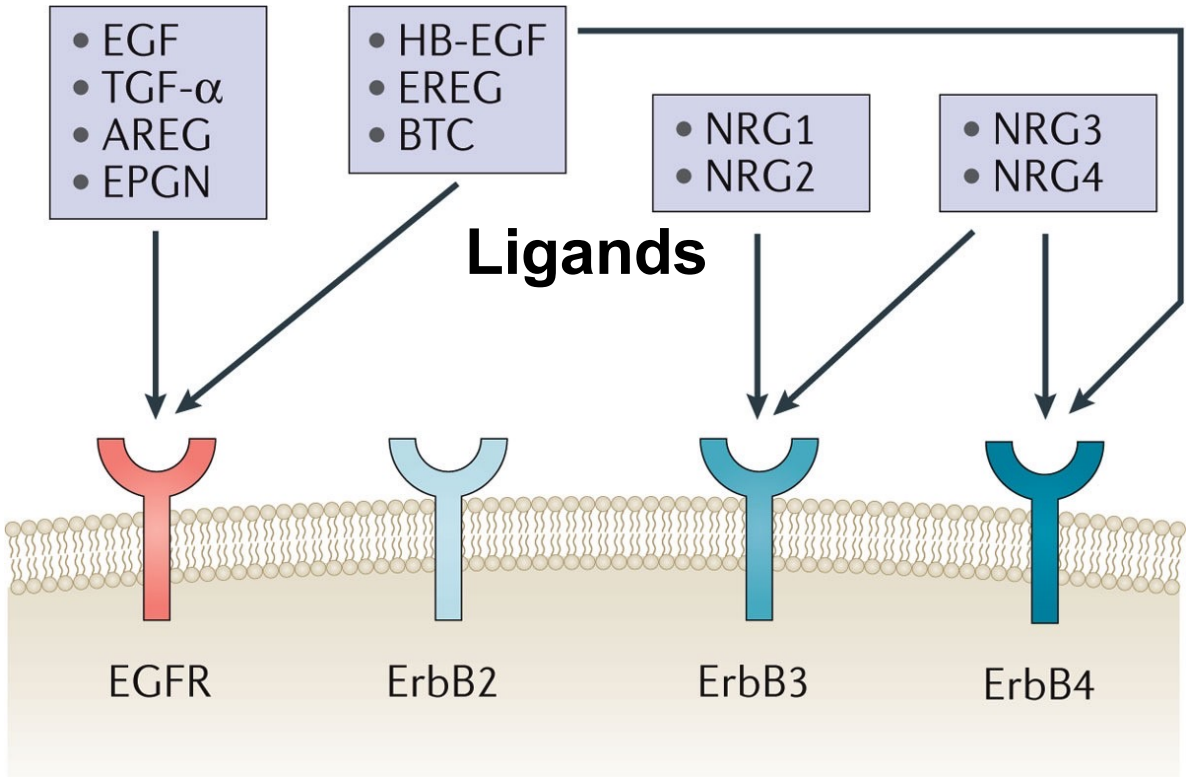
NRG1 AND NTRK IN NSCLC

Endorsed by

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
Conquering Thoracic Cancers Worldwide

Biology of ERBB Family of Transmembrane Receptors in Cancer

Specificity of the various epidermal growth factor (EGF) receptor ligands for the four known ErbB receptors

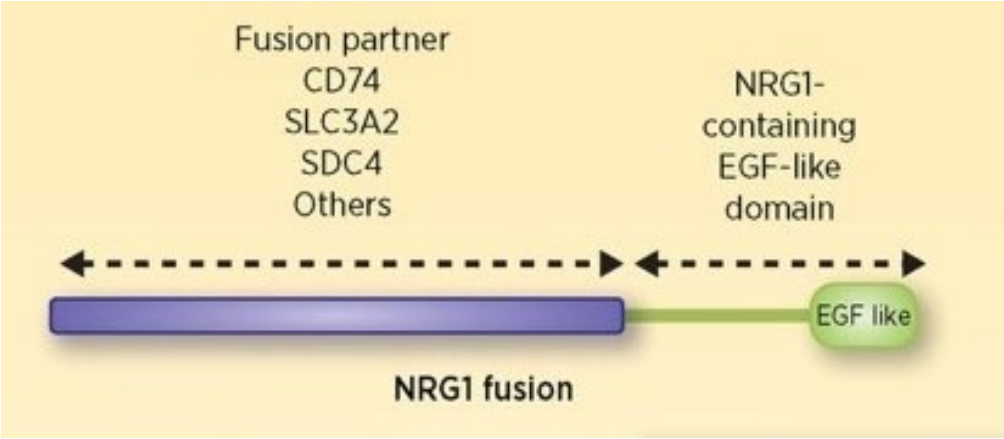


- The ERBB family are receptors for growth factors; they form homo- and heterodimers upon ligands binding.
- The dimers activate downstream pathways, especially MAPK and PI3K/AKT.
- HER2 does not have a cognate ligand and form heterodimers with HER3.
- HER3 binds to EGF-like domain of neuroregulins (NRGs).
- Upon bindings to NRGs, HER3 forms heterodimers with either EGFR and HER2.
- The HER2/HER3 heterodimers exert the strongest downstream signaling activity.

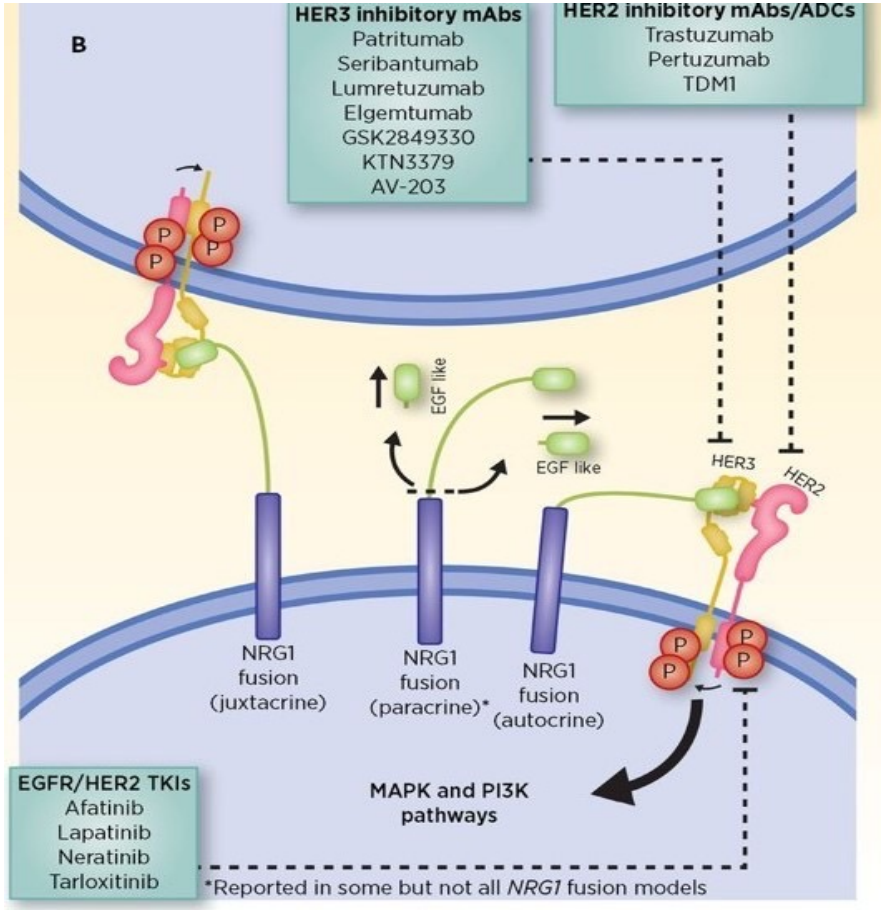
Harskamp LR et al. *Nat Rev Nephrol.* 2016;12(8):496-506.

Role of Neuroregulins in Cancer

- Of the four *NRG* genes, *NRG1* is the best characterized (over 30 isoforms).
- In cancer, gene rearrangements (fusions) have been described in *NRG1* and *NRG2* genes.
- NRG1 fusions exert pro-tumorogenic functions in several cancers, including lung.
- Several gene fusion partners have been described, like *CD74* and *SLC3A2* that fuses with *NRG1* type III-β3 isoform.

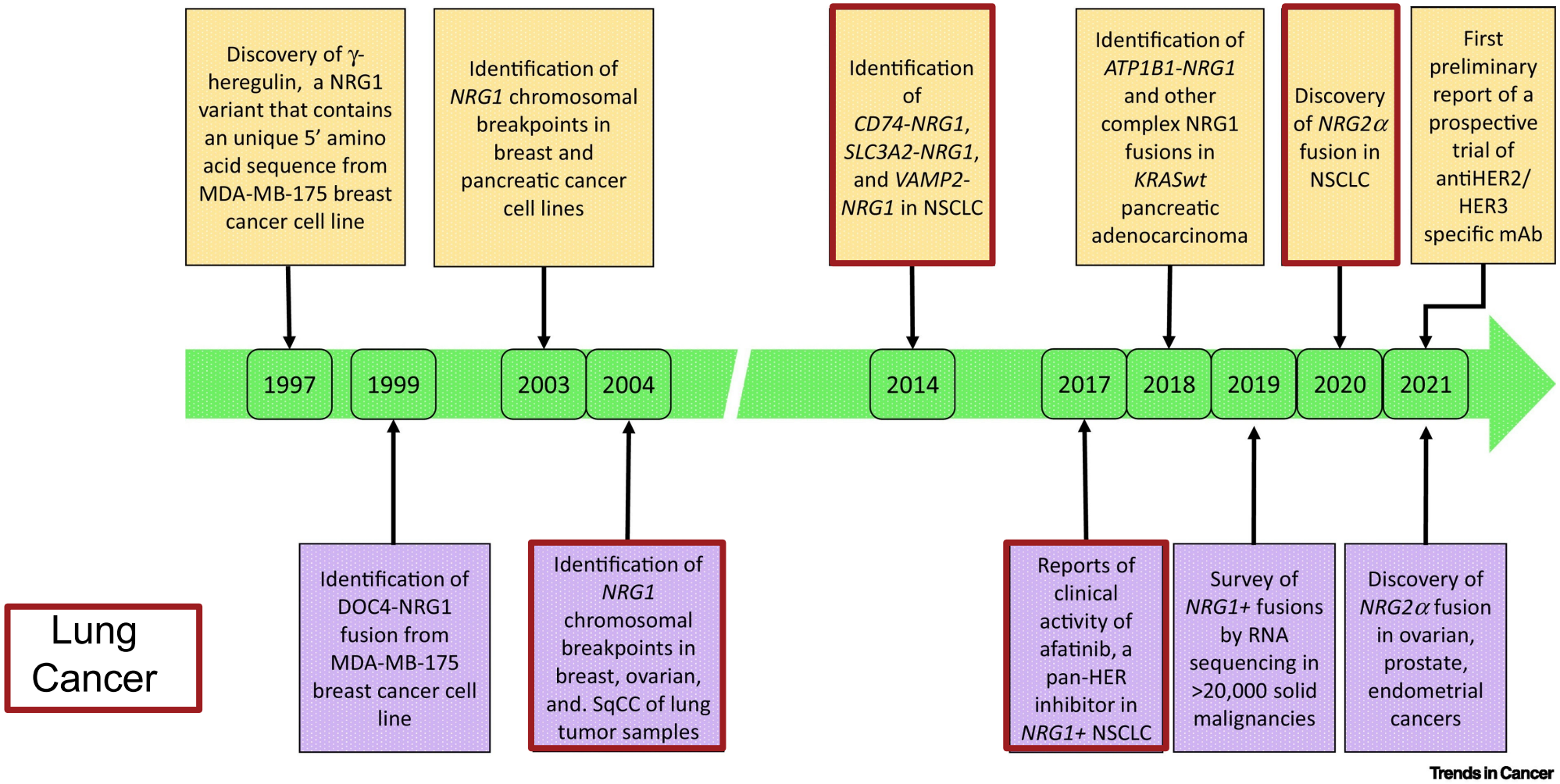


NRG1 EGF-like domain of the fused protein exerts mostly autocrine and juxtacrine activity



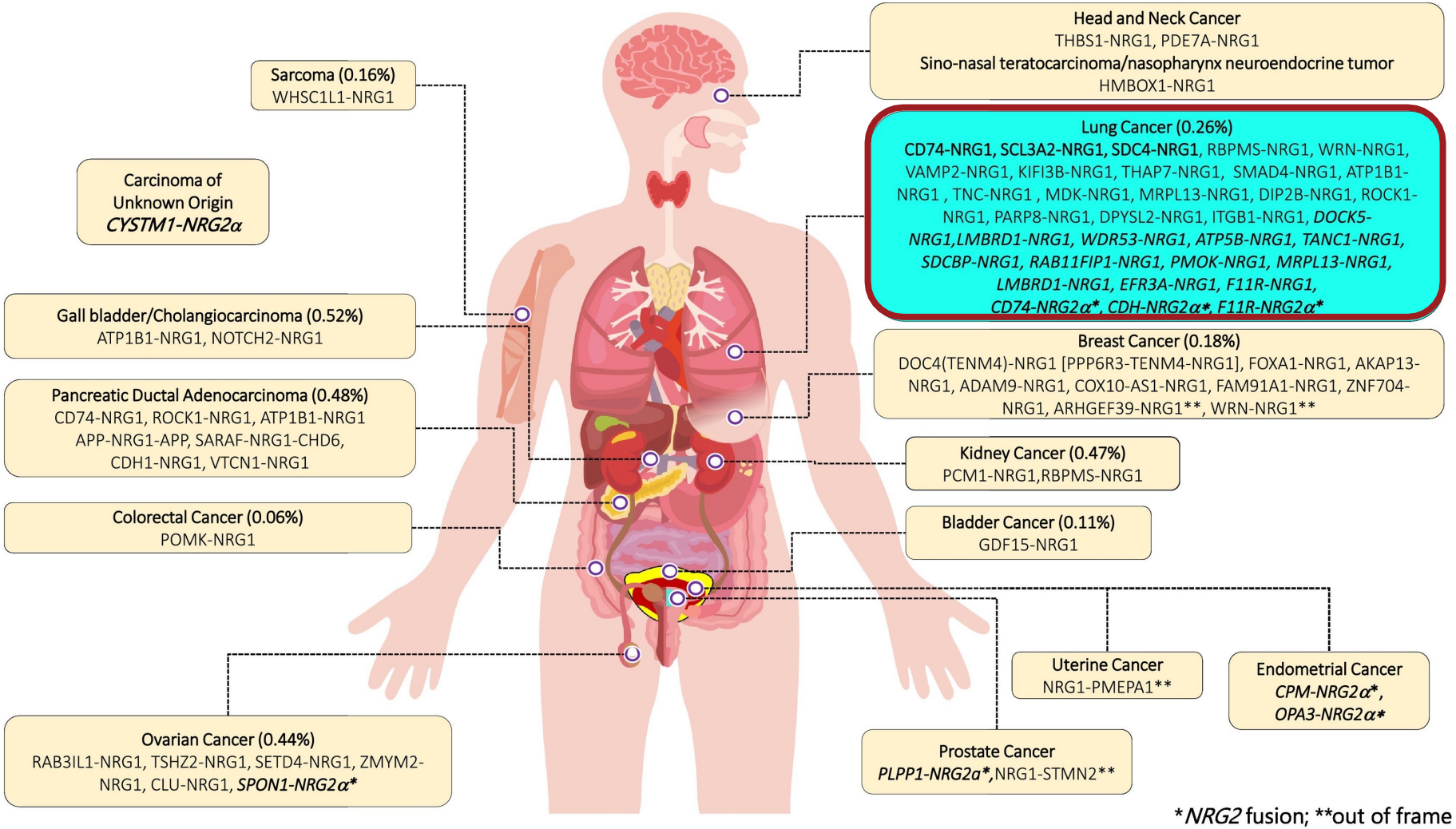
Dimou A, Camidge DR. *Clin Cancer Res.* 2019;25(16):4865-4867.

Timeline of Milestones of *NRG* Fusions in Solid Malignancies



Nagasaka M, Ou SHI. *Trends Cancer.* 2022;8(3):242-258.

NRG Fusions in Solid Malignancies



Lung Cancer 0.3%

Nagasaka M, Ou SHI. *Trends Cancer.* 2022;8(3):242-258.

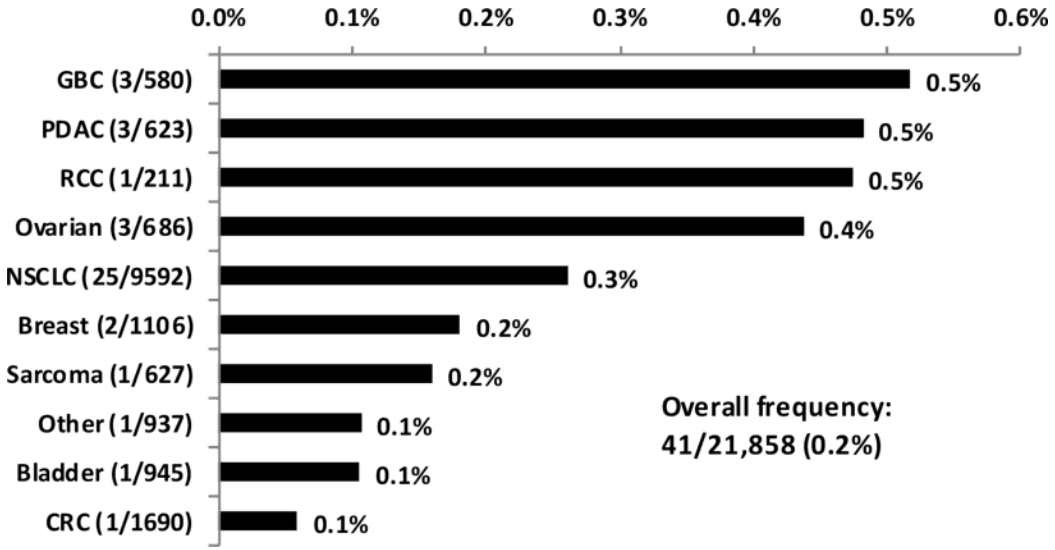
Clinical Characteristics of *NRG1* Fusion Positive Lung Cancers

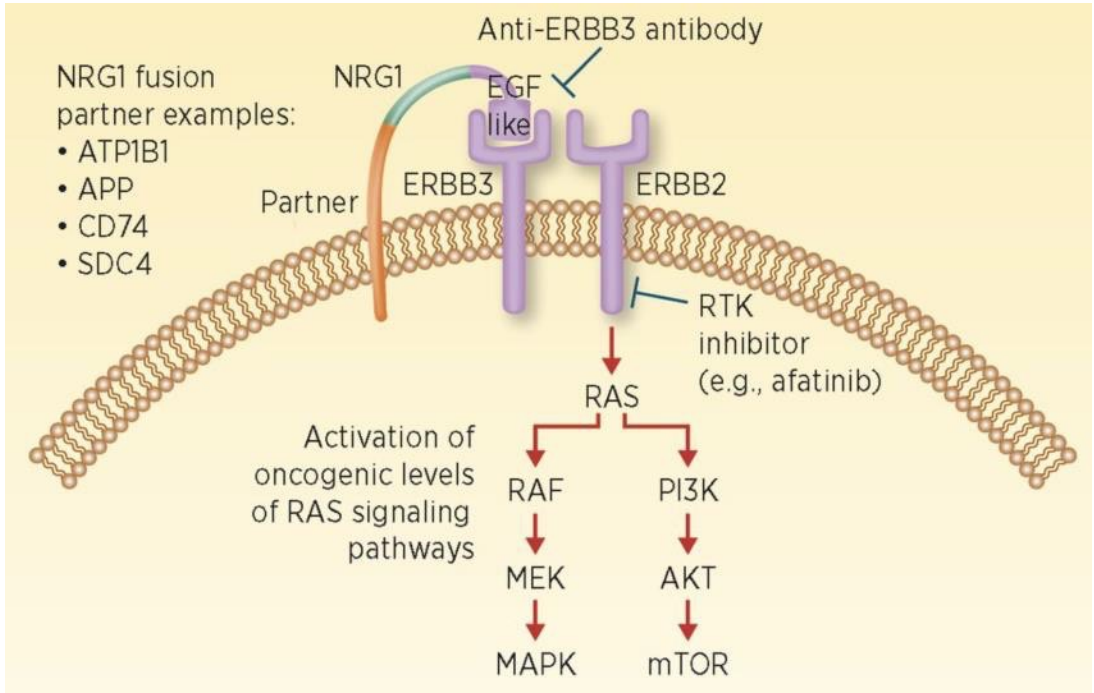
- Detected in non-small cell carcinomas (NSCLC; 0.3%), mostly adenocarcinomas.
- More frequent in invasive mucinous adenocarcinomas (IMAs 37% of *NRG1*-fusion+ NSCLCs) than other subtypes.
- More frequent in never smokers (57%) than smokers (43%).
- More frequent in females (59-68%).
- Median age 64-71 years old.

Liu SV et al. *Lung Cancer.* 2021;158:25-28.

NRG1 fusions

- *NRG1* fusions are rare.
  - 0.2% in solid tumors
- NRG1 has an EGF-like domain serving as a ligand to HER3 and HER4.
  - NRG1 binding prompts HER2-HER3 dimerization, resulting in activation of downstream pathways.



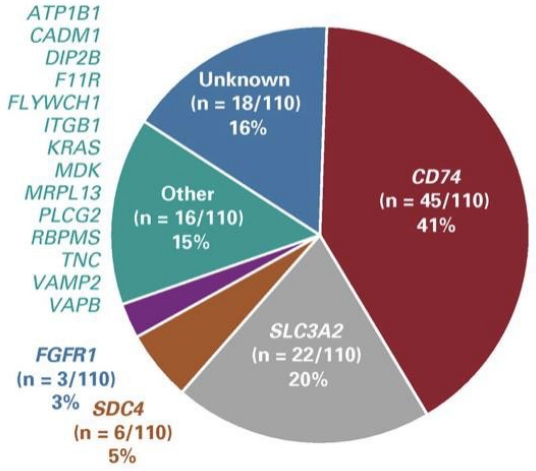


Fernadez-Cuesta et al. *Clin Cancer Res* 2015; Aguirre *Clin Cancer Res* 2019; Jonna at al. *Clin Cancer Res* 2019

NRG1 fusions in NSCLC

- *NRG1* fusions occur in around 0.3% of NSCLC.
- Optimal detection is by RNA based NGS.
  - CD74 is the most common fusion partner.
- Typically, patients are never smokers. Frequently found in invasive mucinous adenocarcinoma.
- Poor response to standard therapies for NSCLC (eNRGy1 Global Multicenter Registry)

Fusion Partners



Activity of Systemic Treatment

Response	Platinum-Doublet–Based Chemotherapy	Taxane-Based Chemotherapy	Combined Chemotherapy and Immune Therapy	Single-Agent Immunotherapy	Targeted Therapy With Afatinib
Response rate, %	13	14	0	20	25
CR, % (n/N)	0 (0/15)	0 (0/7)	0 (0/9)	0 (0/5)	0 (0/20)
PR, % (n/N)	13 (2/15)	14 (1/7)	0 (0/9)	20 (1/5)	25 (5/20)
SD, % (n/N)	47 (7/15)	14 (1/7)	44 (4/9)	20 (1/5)	15 (3/20)
PD, % (n/N)	40 (6/15)	71 (5/7)	56 (5/9)	60 (3/5)	60 (12/20)
Median PFS (95% CI), range	5.8 months (2.2 to 9.8), 0.7-12.1	4.0 months (0.8 to 5.3), 0.8-5.5	3.3 months (1.4 to 6.3), 1.4-15.2	3.6 months (0.9 to undefined), 0.9-11.2	2.8 months (1.9 to 4.3), 0.3-25.3

Drilon et al. *J Clin Oncol* 2021

NRG1 fusions in NSCLC: Therapies in Development

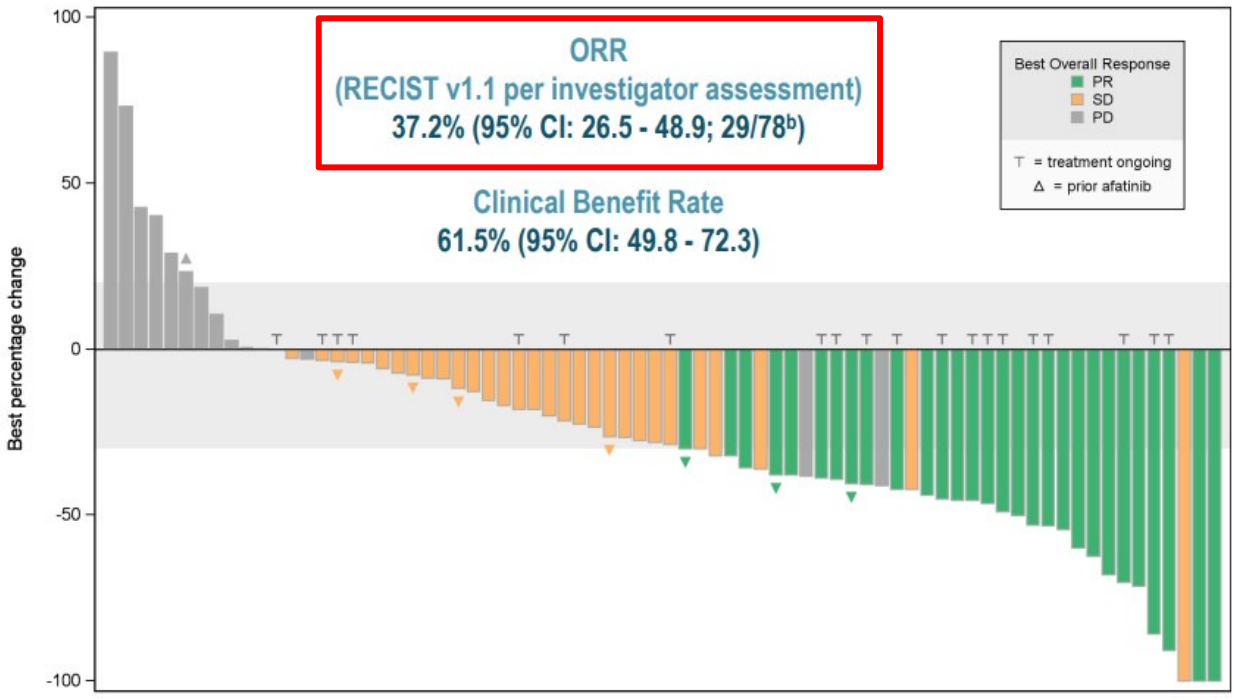
Investigational Agent (Trial Name)	Mode of Action	Phase	Primary Endpoint	N	ORR	NCT
Zenocutuzumab (eNRGy)	Bispecific HER2/HER3 antibody	I/II	ORR	78	37.2%	NCT02912949
Seribantumab* (CRESTONE)	Anti-HER3 monoclonal antibody	II	ORR	18	39%	NCT04383210

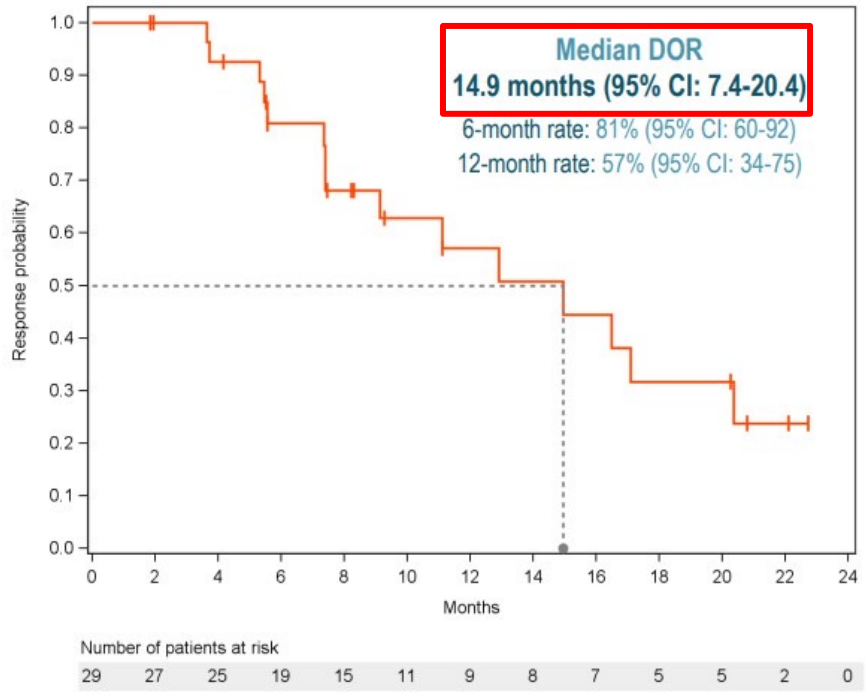
*Development on hold

Schram et al. ESMO 2023; Patil et al. AACR 2023

https://investors.elevationoncology.com/2023-01-06-Elevation-Oncology-Announces-Pipeline-Prioritization,-Realignment-of-Resources-to-Advance-EO-3021-and-CEO-Transition

Zenocutuzumab Activity in NRG1+ NSCLC





Schram et al. ESMO 2023

Safety Profile of Zenocutuzumab

	Related TEAEs (≥10% patients and all Grade 3-4) n (%)		TEAEs Irrespective of Causality (≥10% patients and all Grade 3-4) n (%)	
	All grades	Grades 3-4	All grades	Grades 3-4
≥1 TEAE	115 (61)	11 (6)	166 (88)	66 (35)
Diarrhea	33 (17)	3 (2)	53 (28)	4 (2)
Infusion-related reactions[b]	23 (12)	0	23 (12)	0
Fatigue	18 (10)	0	30 (16)	4 (2)
Nausea	16 (8)	2 (1)	30 (16)	3 (2)
Vomiting	11 (6)	1 (1)	21 (11)	1 (1)
Anemia	7 (4)	1 (1)	29 (15)	7 (4)
Constipation	5 (3)	0	24 (13)	0
ALT increased	5 (3)	1 (1)	18 (10)	5 (3)
AST increased	5 (3)	2 (1)	14 (7)	5 (3)
Decreased appetite	5 (3)	1 (1)	16 (8)	2 (1)
Abdominal pain	3 (2)	1 (1)	21 (11)	4 (2)
Dyspnea	2 (1)	0	24 (13)	6 (3)
GGT increased	2 (1)	1 (1)	13 (6)	6 (3)
Platelet count decreased	2 (1)	1 (1)	4 (2)	1 (1)
Hyperuricemia	2 (1)	1 (1)	3 (2)	1 (1)
Bacteremia	1 (1)	1 (1)	2 (1)	2 (1)
Hypertransaminasemia	1 (1)	1 (1)	1 (1)	1 (1)

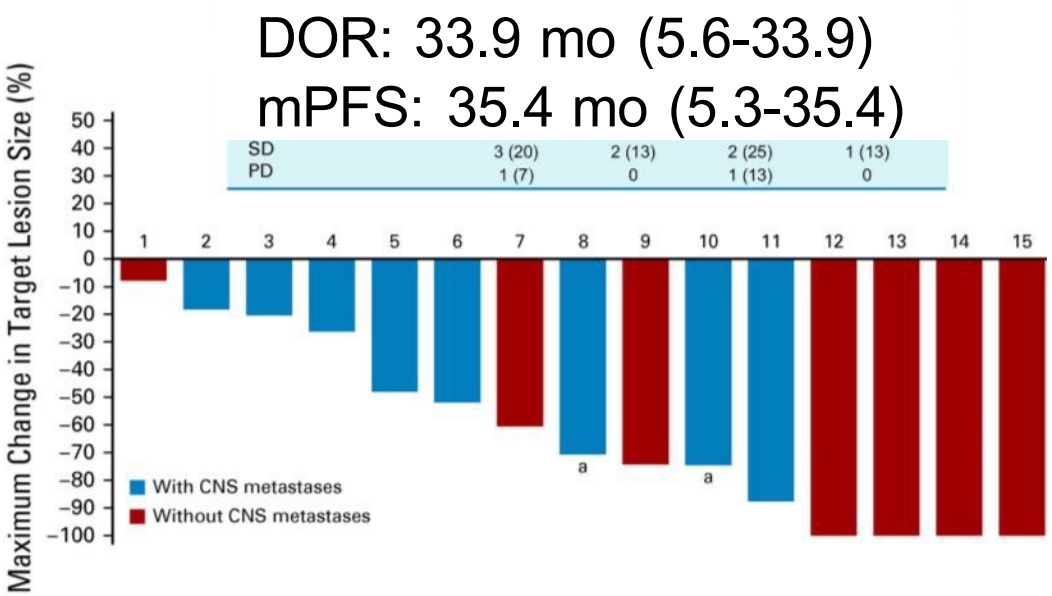
- N=189
- Low incidence of grade 3 or 4 TRAEs
- No patient discontinued treatment due to TRAEs
- Infusion-related reactions in 12% (no grade ≥3 events)

Schram et al. ESMO 2023

NTRK fusion-positive NSCLC

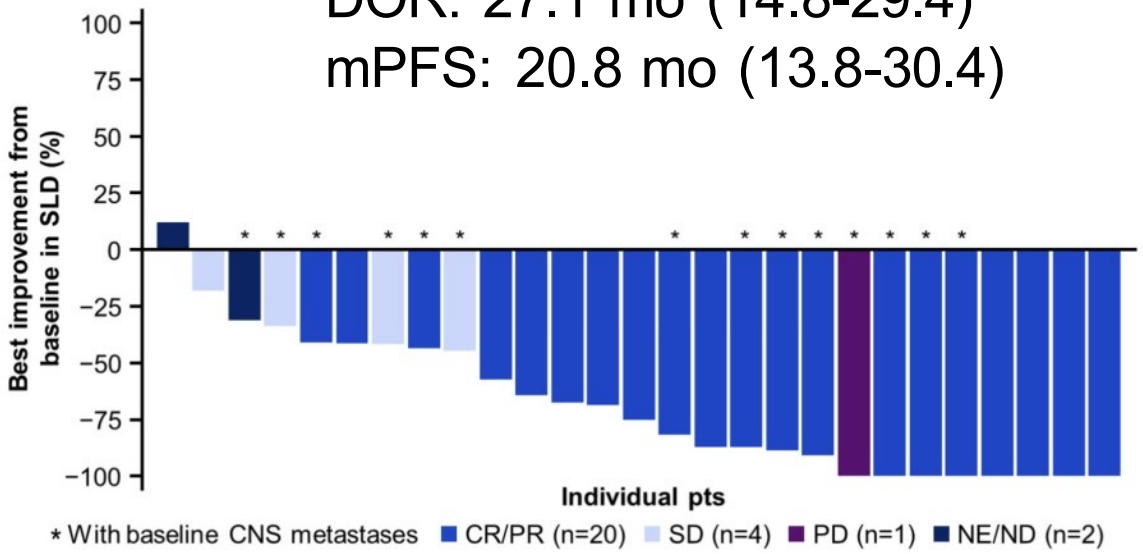
Larotrectinib (N=20)

ORR: 73%
DOR: 33.9 mo (5.6-33.9)
mPFS: 35.4 mo (5.3-35.4)



Entrectinib (N=31)

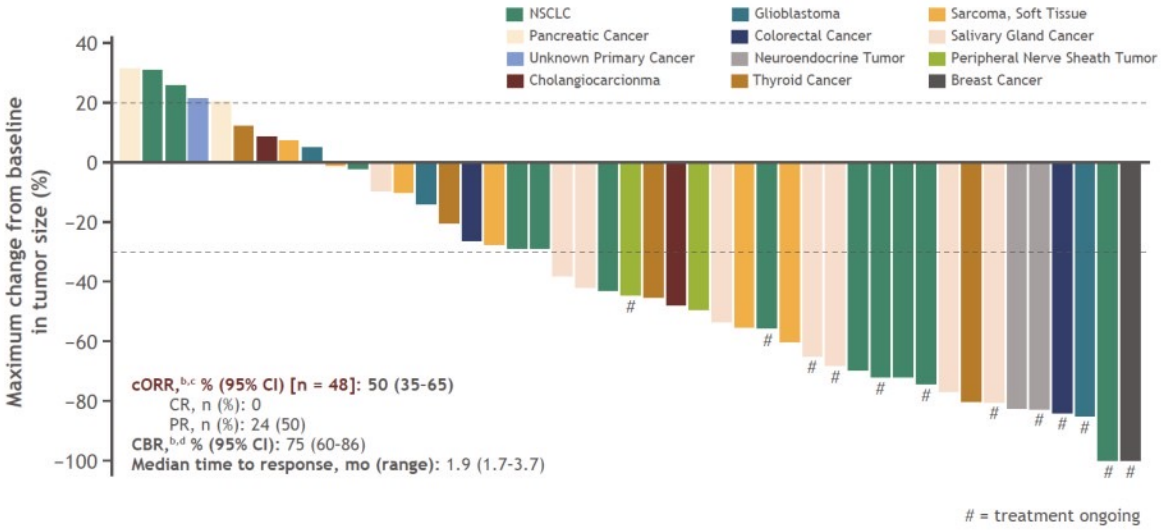
ORR: 64.5%
DOR: 27.1 mo (14.8-29.4)
mPFS: 20.8 mo (13.8-30.4)



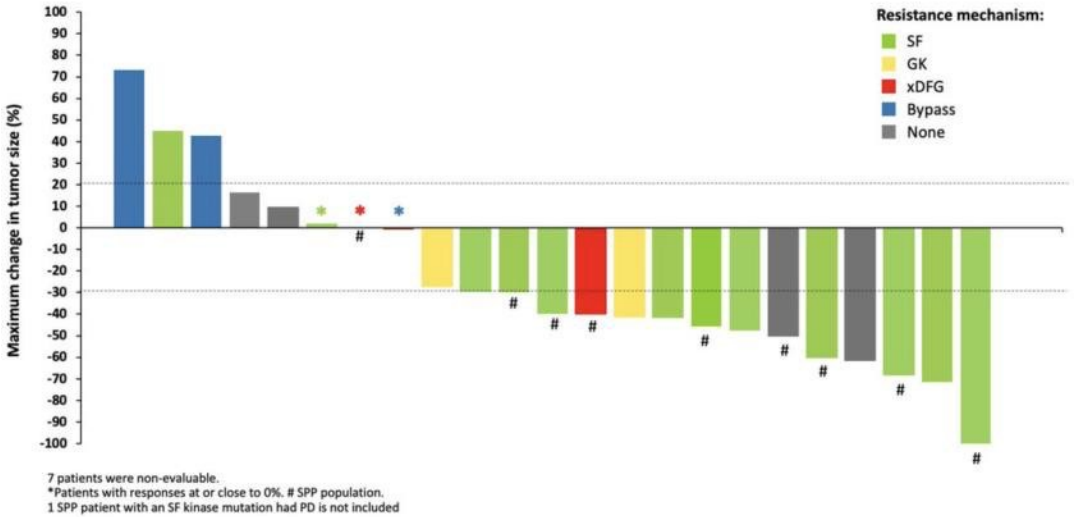
Drilon et al. *JCO Precis Oncol* 2022; Cho et al. ASCO 2023

Clinical Activity of Next-generation TRK Inhibitors in TRK TKI-Pretreated Solid tumors

Repotrectinib



Selitrectinib



Solomon ESMO 2023; Hyman AACR 2019

Select Next-generation TRK Inhibitors

Agent	Targets	Phase	NCT
Selitrectinib	Selective TRK inhibitor	I/II	NCT03215511
Repotrectinib	TRK and ROS1 inhibitor	I/II	NCT03093116 NCT04094610
Taletrectinib	TRK and ROS1 inhibitor	I/II	NCT02675491 NCT04617054
SIM1803–1A	TRK and ROS1 inhibitor	I	NCT04671849
PBI-200	Selective TRK inhibitor	I/II	NCT04901806
TY-2136b	TRK, ROS1, ALK inhibitor	I	NCT05769075

Harada and Drilon *Cancer Genet* 2022; Clinicaltrials.gov

Conclusions

- Molecular profiling should be performed comprehensively to identify rare but crucial alterations.
- The treatment landscape for driver-positive NSCLC is continually evolving, with the active development of novel therapeutics.
- In the future, it's anticipated that these therapies will be increasingly included in earlier stages of the disease.

The End

Thanks,!!